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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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R C van Dijk



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2-Aryl-acetic acids, their derivatives and pharmaceutical compositions containing them

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"2-ARYL-ACETIC ACIDS, THEIR DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

Brief description of the invention

The present invention relates to 2-arylacetic acids and derivatives thereof, and to pharmaceutical compositions containing them, which are used in the prevention and treatment of tissue damage due to the exacerbated recruitment of polymorphonucleated neutrophils (PMN leukocytes) at inflammation sites. In particular, the invention is directed to 2-phenylacetic acids and derivatives thereof for the treatment of IL-8 mediated diseases, such as psoriasis, ulcerative colitis, COPD and of the damages caused by ischemia and reperfusion.

Background of the invention

Particular blood cells (macrophages, granulocytes, neutrophils, polymorphonucleated), when stimulated by substances called chemokines respond to a chemical stimulus, by migrating along the concentration gradient of the stimulating agent, through a process called chemotaxis. The main known stimulating agents or chemokines are represented by the breakdown products of complement C5a, some N-formyl peptides generated from lysis of the bacterial surface or peptides of synthetic origin, such as formyl-methionyl-leucyl-phenylalanine (f-MLP) and mainly by a variety of cytokines, including Interleukin-8 (IL-8, also referred to as CXCL8). Interleukin-8 is an endogenous chemotactic factor produced by most nucleated cells such as fibroblasts, macrophages, endothelial and epithelial cells subjected to the TNF- α (Tumor Necrosis Factor) stimulus, interleukins IL-1 α and IL-1 β and bacterial wall lipopolysaccharides (LPS), as well as the same neutrophils exposed to the action of LPS or N-formyl peptides of bacterial origin (f-MLP). Belonging to the family of this chemotactic factor [also known as neutrophil activating factor (NAF), T-lymphocyte chemotactic factor, monocyte derived neutrophils chemotactic factor (MDNCF)] is a series of IL-8-like chemokines [GRO α , β , γ and NAP-2], which bind to the IL-8 receptors (Chang et al., J. Immunol., 148, 451, 1992). Neutrophils are the first line of defense against bacterial infection, owing to the ability of these cells to migrate from the peripheral blood through the endothelial junctions and the tissue matrices towards the action sites (i.e. along chemotactic factor concentration gradients) where they act by attacking the microorganisms, removing damaged cells and repairing tissues (M.A. Goucerot-Podichlo et al., Pathol. Biol (Paris), 44, 36, 1996).

In some pathological conditions, marked by exacerbated recruitment of neutrophils, a more severe tissue damage at the site is associated with the infiltration of neutrophilic cells. Recently, the role of neutrophilic activation in the determination of damage associated with post ischemia reperfusion and pulmonary hyperoxia was widely demonstrated.

5 Experimental models [N. Sekido et al., *Nature*, 365, 654, 1993 and T. Matsumoto et al., *Lab. Investig.*, 77, 119, 1997] and clinical studies [A. Mazzone et al., *Recent Prog. Med.*, 85, 397, 1994; G. Receipts et al., *Atheroscl.*, 91, 1, 1991] have shown the direct correlation between cellular damage and the extent of PMN leukocyte infiltration, IL-8 being the most specific and powerful activator thereof. In patients affected by acute respiratory
10 insufficiency (ARDS), the exacerbated recruitment of neutrophils in the airways and in pulmonary fluids can be closely correlated with the concentration of the cytokine IL-8 (E.J. Miller et al., *Am. Rev. Respir. Dis.*, 146, 437, 1992) and with the severity of the pathology (Kurodowska et al., *Immunol.*, 157, 2699, 1996). Treatment with anti-IL-8 antibody was shown to be effective in models of acute respiratory insufficiency and pulmonary damage
15 caused by endotoxemia (K. Yokoi et al., *Lab. invest.*, 76, 375, 1997).

The specific role of IL-8 in causing damage following post ischemia reperfusion in patients affected by acute myocardium infarction was shown (Y. Abe et al., *Br. Heart J.*, 70, 132, 1993); the key role exerted by IL-8 in the mediation of the damage associated with the post ischemia reperfusion is corroborated also by the results obtained using the anti-IL-8
20 antibody in an experimental model of focal cerebral ischemia in rabbits (T. Matsumoto et al., *Lab. invest.*, 77, 119, 1997).

The biological activity of IL-8 is mediated by the interaction of the interleukin with CXCR1 and CXCR2 membrane receptors which belong to the family of seven transmembrane receptors, expressed on the surface of human neutrophils and of certain
25 types of T-cells (L. Xu et al., *J. Leukocyte Biol.*, 57, 335, 1995).

Although CXCR1 activation is known to play a crucial role in IL-8-mediated chemotaxis, it has been recently supposed that CXCR2 activation could play a pathophysiological role in chronic inflammatory diseases such as psoriasis. In fact, the pathophysiological role of IL-8 in psoriasis is also supported by the effects of IL-8 on keratinocyte functions.

30 Indeed, IL-8 has been shown to be a potent stimulator of epidermal cell proliferation as well as angiogenesis, both important aspects of psoriatic pathogenesis (A. Tuschil et al., *J. Invest Dermatol.*, 99, 294, 1992; Koch AE et al., *Science*, 258, 1798, 1992). Additionally,

IL-8 induced the expression of the major histocompatibility complex II (MHC-II) moiety HLA-DR on cultured keratinocytes (L. Kemény et al., *Int Arch Allergy Immunol*, 10, 351, 1995). The effect of CXCL8 on keratinocyte function is supposed to be mediated by CXCR2 activation.

5 In agreement with this hypothesis, it was reported that CXCR2 is overexpressed in epidermal lesional skin of psoriatic patients (R. Kulke et al., *J. Invest. Dermatol.*, 110, 90, 1998).

In addition, there is accumulating evidence that the pathophysiological role of IL-8 in melanoma progression and metastasis could be mediated by CXCR2 activation.

10 The potential pathogenetic role of IL-8 in cutaneous melanoma is independent on its chemotactic activity on human PMNs. In fact, IL-8 is supposed to act as an autocrine growth and metastatic factor for melanoma cells.

Consistent amount of CXCL8 have been found to be produced by melanoma cells and melanoma tumor cells are known to express immunoreactive CXCR2 receptor (L.R. Bryan et al., *Am J Surg*, 174, 507, 1997). IL-8 is known to induce haptotactic migration as well as proliferation of melanoma cells (J.M. Wang et al., *Biochem Biophys Res Commun*, 169, 165, 1990).

Potential pathogenic role of IL-8 in pulmonary diseases (lung injury, acute respiratory distress syndrome, asthma, chronic lung inflammation, and cystic fibrosis) and, specifically, in the pathogenesis of COPD (chronic obstructive pulmonary disease) through the CXCR2 receptor pathway has been widely described (D. WP. Hay and H.M. Sarau., *Current Opinion in Pharmacology* 2001, 1:242-247).

20 Phenylureido compounds have been described, which can selectively antagonize the binding of IL-8 to the CXCR2 receptor (J.R. White et al., *J. Biol. Chem.*, 273, 10095, 1998); the use of these compounds in the treatment of pathological states mediated by Interleukin-8 is in fact claimed in WO 98/07418.

25 Studies on the contribution of single (S) and (R) enantiomers of ketoprofen to the anti-inflammatory activity of the racemate and on their role in the modulation of the chemokine have demonstrated (P. Ghezzi et al., *J. Exp. Pharm. Ther.*, 287, 969, 1998) that the two enantiomers and their salts with chiral and non-chiral organic bases can inhibit in a dose-dependent way the chemotaxis and increase in intracellular concentration of Ca^{2+} ions induced by IL-8 on human PMN leukocytes (U.S. Patent 6,069,172). It has been

subsequently demonstrated (C. Bizzarri et al., Biochem. Pharmacol. 61, 1429, 2001) that Ketoprofen shares the inhibition activity of the biological activity of IL-8 with other molecules belonging to the class of non-steroidal anti-inflammatory phenylpropionic acids, such as flurbiprofen and ibuprofen. The cyclo-oxygenase enzyme (COX) inhibition activity typical of said drugs limits the therapeutical application of these compounds in the context of the treatment of neutrophil-dependent pathological states and inflammatory conditions such as psoriasis, idiopathic pulmonary fibrosis, acute respiratory failure, damages from reperfusion and glomerulonephritis. The inhibition of prostaglandin synthesis deriving from the action on cyclo-oxygenase enzymes involves the increase of the cytokine production, which, like TNF- α , play a role in amplifying the undesired pro-inflammatory effects of neutrophils.

It has been demonstrated that derivatization of the carboxylic function in arylpropionic acids allows to obtain potent IL-8 inhibitors which show the required selectivity with respect to the COX inhibitory effect.

Structure Activity Relationship studies performed in the class of 2-phenylpropionic acid derivatives led to the identification of novel classes of potent and selective inhibitors of IL-8 biological activities suitable for "in vivo" administration.

R-2-arylpropionic acid amides and N-acylsulfonamides have then been described as effective inhibitors of IL-8 induced neutrophils chemotaxis and degranulation (WO 01/58852; WO 00/24710). Furthermore, novel subclasses of R and S 2-phenylpropionic acids have been described (PCT/EP02/12939) as potent IL-8 inhibitors completely lacking the undesired COX inhibitory effect.

Detailed description of the invention

Medicinal Chemistry studies have shown the crucial role of the methyl group on the propionic chain of 2-arylpropionic acids in order for them to exert their IL-8 inhibitory activity.

We have, in fact, found that 2-[4-isobutylphenyl]acetic acid (ibufenac) and 2-[3-benzoylphenyl]acetic acid (ketofenac), well known COX inhibitors belonging to the family of phenylacetic acids, do not exert any IL-8 inhibitory activity which is present, instead, in the potent corresponding phenylpropionic acids, such as ibuprofen and ketoprofen.

In general, 2-phenylacetic acids and their derivatives, such as amides and sulfonamides, lack any IL-8 inhibitory activity and this confirms the crucial role of the methyl group in the corresponding 2-phenylpropionic derivatives.

We have completed SAR studies on the different classes of 2-arylpropionic acids and derivatives described above, which allowed to exactly clarify the pharmacophore structure shared by all these novel classes of IL-8 inhibitors.

A pharmacophore is defined as the ensemble of steric and electronic requirements, in a class of biologically active compounds, necessary to ensure the biological activity; in general, the pharmacophore can be considered the ensemble of steric and electronic requirements necessary to ensure positive interactions between a biologically active molecule and its target. The assumption, in a pharmacophore study, is that all compounds in a training set share the same mechanism and interact with the same biological target.

We have now defined two pharmacophore models: a first model accounting for the biological activity of IL-8 inhibitors selectively acting on CXCR1 mediated pathway (hereinafter CXCR1 inhibitors), and a second model representing the steric and electronic requirements of the IL-8 inhibitors dually acting on CXCR1 and CXCR2 mediated pathway (hereinafter CXCR1/CXCR2 inhibitors). These two models account for the observed Structure Activity Relationships since all the inactive molecules tested against the two complete pharmacophore hypothesis either miss crucial features superimposition (unfit) or fit the pharmacophore hypothesis in a high energy conformations. The two newly found pharmacophore models share four out of respectively five and six features, these four features are completely superimposable in the 3D chemical space. An outline of the common portion of the pharmacophore models is illustrated in Figure 1.

Description of the figures

Figure 1 graphically shows the four common features of the pharmacophores of respectively CXCR1 inhibitors and CXCR1/CXCR2 inhibitors. The following features types take part in the pharmacophore portion: two Hydrogen Bond Acceptors, one Hydrophobic Aromatic and one Hydrophobic Aliphatic. The (aromatic and aliphatic) hydrophobic features are represented by spheres of 1.7 Angstroms radius. The hydrogen bond acceptor is represented by a vector function consisting two spheres whose centroids are 3.0 Angstroms apart. The smaller (1.7 Angstroms radius) sphere defines the position of the hydrogen bond acceptor atom on the ligand and the larger sphere (2.3 Angstroms)

defines the projected point of the hydrogen bond acceptor from the receptor site. The solid sphere represents the exact location in the 3D space of the methyl group of the phenylpropionic moiety.

Figure 2 illustrates superimposition of the following Arylpropionic derivatives: R(-)-2-(4-isobutylphenyl) propionic acid; R(-)-2-(4-isobutylphenyl)propionyl methanesulphonamide; R(-)-N-(2'-hydroxyethoxyethyl)-2-(4-isobutylphenyl)propionamide. The solid sphere represents the exact location in the 3D space of the methyl group of the phenylpropionic moiety.

Figure 3 illustrates superimposition of the following Arylacetic derivatives: (2-methyl-4-isobutylphenyl)acetic acid; (2-methyl-4-isobutylphenyl) acetyl methanesulphonamide; (2-methyl-4-isobutylphenyl)acetamide.

Figure 4 illustrates superimposition of the following Arylacetic derivatives: (5-benzoyl-1-methyl-1H-pyrrol-2-yl)acetic acid; (1-benzoyl-2-methyl-1H-indol-3-yl)acetyl methanesulphonamide; (2-chloro-3-benzoylphenyl)acetamide.

Pharmacophore generation has been performed using the CatalystTM software, version 4.7 (Molecular Simulations, Inc., San Diego, CA), which is designed to identify common configurations of the active molecules by means of their chemical features. A configuration is a set of relative locations in 3D space, each associated with a feature type. All the compounds in the training set were described in terms of their chemical functions associated within the 3D space. Furthermore, each chemical moiety can be considered by the software as more than one feature on the basis of the found similarity. For example, an aromatic ring can "establish" both hydrophobic interactions and π - π interactions in the target site and this different behaviour is referred to different features (Hydrophobic, Hydrophobic aromatic).

A functional group in a molecule can be associated to more than one feature, depending on its chemical and physical properties, and different functional groups can show behaviour similarity in the interaction with the target so mapping the same feature.

Analysis of the feature definitions and selection of the features is a crucial step in the pharmacophore hypothesis generation. It is well known that the most important forces involved in molecular recognition are represented by electrostatic interactions, hydrogen bonding and hydrophobic interactions. We adopted several features definitions relating the

chemical nature of the group to the ability of engaging specific interactions responsible for the biological activity.

FEATURES DEFINITIONS

HYDROGEN BOND ACCEPTOR (HBA) (lipid)

- 5 A Hydrogen bond acceptor lipid feature matches the following types of atoms or groups of atoms which are surface accessibility: nitrogens, oxygens, or sulphurs (except hypervalent) that have a lone pair and charge less than or equal to zero.

Since a lipid environment was considered, all basic amines (primary, secondary and tertiary) are included in this definition. The hydrogen bond is a highly directional
10 interaction, this feature is so indirectly linked to the theoretic position of the corresponding hydrogen donor. Three hydrogen bonds positions are for instance considered on carbonyl group (acceptor), the first two along the ideal positions of the lone pairs and a third one along the C=O bond direction.

HYDROPHOBIC (aliphatic, aromatic)

- 15 Hydrophobic feature is defined as a contiguous set of atoms that are not adjacent to any concentrations of charge (charged atoms or electronegative atoms), in a conformer such that the atoms have surface accessibility, including phenyl, cycloalkyl, isopropyl, and methyl.

Nevertheless it has been necessary to distinguish the aromatic hydrophobic feature from the
20 aliphatic one in order to grant a good fitting with biological results. The former considers only the aromatic atoms, the latter considers only the aliphatic atoms.

A molecule is considered matching a configuration only if possesses a set of relative features and specific conformation such that its features can be superimposed with the corresponding "ideal" locations. A set of features can be considered superimposed if each
25 feature lies within a specific distance on tolerance, from the ideal point.

The absolute sphere centroids co-ordinates of each feature are listed below:

HYDROPHOBIC AROMATIC has Cartesian co-ordinates +2.588, +0.613, -1.940 respectively along XYZ axes.

HYDROPHOBIC ALIFATIC has Cartesian co-ordinates of +1.788, +2.693, +1.260
30 respectively along XYZ axes.

HYDROGEN BOND ACCEPTOR PROJECTED POINT 1 has Cartesian co-ordinates of -2.713, +2.333, +2.840 respectively along XYZ axes.

HYDROGEN BOND ACCEPTOR ORIGIN 1 has Cartesian co-ordinates of -0.233, +0.936, +1.877 respectively along XYZ axes.

HYDROGEN BOND PROJECTED ACCEPTOR POINT 2 (optional) has Cartesian co-ordinates of -5.013, -1.188, -0.400 respectively along XYZ axes.

5 HYDROGEN BOND ACCEPTOR ORIGIN 2 (optional) has Cartesian co-ordinates of -2.688, -1.514, +1.472 respectively along XYZ axes.

Mapping of the first three features (HYDROPHOBIC ALIPHATIC, HYDROPHOBIC AROMATIC, HYDROGEN BOND ACCEPTOR 1) is crucial for the biological IL-8 inhibitory activity of the class; the fourth feature (HYDROGEN BOND
10 ACCEPTOR 2) can be optionally mapped by the molecules of the class but the presence of the second hydrogen bond acceptor group is not indispensable.

Tolerances on all the distances between the chemical features have been established in + 0.5 Angstroms and tolerances on the geometric angles \pm 20 degrees.

As previously discussed, other pharmacophore points are required in order to
15 complete the pharmacophore analysis but their description is not relevant for the purposes of present invention. The observed CXCR1/CXCR2 selectivity in the class is strictly related to the ability of the inhibitors to match specific points in the non-common part of the pharmacophore.

On the contrary, as far as the common part of the pharmacophore is concerned, a
20 general superimposition mode is observed for CXCR1 inhibitors and CXCR1/CXCR2 inhibitors belonging to the classes of 2-phenylpropionic acids, 2-phenylpropionyl sulphonamides and 2-phenylpropionamides as outlined in Figure 2. The solid sphere represents the exact location in the 3D space of the methyl group of the phenylpropionic moiety.

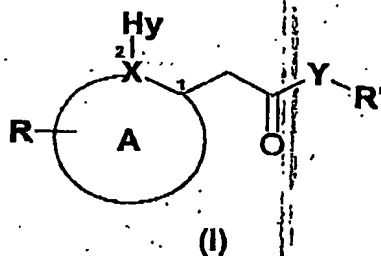
25 In the retrieved ligands which partially or fully map this hypothesis (Figure 2) the phenyl residue of the 2-phenylpropionic chemical structure always matches very well the HYDROPHOBIC AROMATIC feature; the HYDROGEN BOND ACCEPTOR (HBA) 1 feature is consistently well matched by the carbonylic oxygen of the propionyl residue; the HYDROGEN BOND ACCEPTOR (HBA) 2 feature can be optionally matched by a second
30 Hydrogen Bond Acceptor atom on the residue linked at the amidic or sulphonamidic nitrogen; the HYDROPHOBIC ALIPHATIC feature is invariably matched by the methyl group of the propionyl residue. Phenylacetic acids and derivatives, on the basis of the

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above considerations, obviously fail to match the pharmacophore hypothesis, since the crucial HYDROPHOBIC ALIPHATIC feature, represented by the solid sphere in Figure 2, is missing in their chemical structure.

We have now found out that selected subclasses of 2-arylacetic acids and derivatives thereof, which lack the methyl group of the propionyl residue, show the surprising ability to effectively inhibit IL-8 induced neutrophils chemotaxis and degranulation.

The present invention thus provides 2-arylacetic acids and derivatives of formula (I):



and pharmaceutically acceptable salts thereof,
wherein

A includes the X atom and represents a 5-6 membered aromatic or heteroaromatic ring optionally including a heteroatom, or a further heteroatom when X is N, selected from N (nitrogen), O (oxygen), S (sulfur); the 5-6 membered aromatic or heteroaromatic ring is optionally fused with a second ring to give bicyclic aromatic or heteroaromatic structures; labels 1 and 2 mark the relevant positions on the A ring;

the X atom is selected from N (nitrogen) and C (carbon);

R is a substituting group on the A ring selected from:

- a group in the 3 (meta) position selected from a linear or branched C₁-C₅ alkyl, C₂-C₅-alkenyl or C₂-C₅-alkynyl group, substituted or not-substituted phenyl, linear or branched C₁-C₅ hydroxyalkyl, C₂-C₅-acyl, substituted or not-substituted benzoyl;
- a group in the 4 (para) position selected from C₁-C₅ alkyl, C₂-C₅-alkenyl or C₂-C₅-alkynyl group, C₃-C₆-cycloalkyl, C₁-C₅-acyloxy, substituted or not-substituted benzoyloxy, C₁-C₅-acylamino, substituted or not-substituted benzoylamino, C₁-C₅-sulfonyloxy, substituted or not-substituted benzenesulfonyloxy, C₁-C₅-alkanesulfonylamino, substituted or not-substituted benzenesulfonylamino, C₁-C₅-alkanesulfonylmethyl, substituted or not-substituted benzenesulfonylmethyl, 2-furyl; 3-

tetrahydrofuryl; 2 thiophenyl; 2-tetrahydrothiophenyl groups or a C_1 - C_8 -alkanoyl, cycloalkanoyl, or arylalkanoyl- C_1 - C_5 -alkylamino group, such as acetyl-N-methyl-amino, pivaloyl-N-ethyl-amino group;

Hy is a small hydrophobic group with a steric hindrance factor ν ranging between 0.5 and

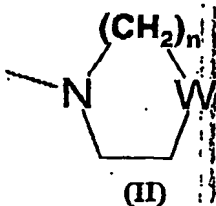
5 0.9 Å (where ν is the Charton steric constant for substituents), including methyl, ethyl, chlorine, bromine, methoxy, trifluoromethyl;

The Y group is selected from O (oxygen) and NH;

when Y is O (oxygen), R' is H (hydrogen);

When Y is NH, R' is selected from

- 10 - H, C_1 - C_5 -alkyl, C_1 - C_5 -cycloalkyl, C_1 - C_5 -alkenyl;
- an amino acid residue consisting of straight or branched C_1 - C_6 -alkyl, C_1 - C_6 -cycloalkyl, C_1 - C_6 -alkenyl, phenylalkyl substituted with one or more carboxy (COOH) groups;
- an amino acid residue consisting of straight or branched C_1 - C_6 -alkyl, C_1 - C_6 -cycloalkyl, C_1 - C_6 -alkenyl, phenylalkyl bearing along the chain a heteroatom selected from oxygen
- 15 and sulfur and with one or more carboxy (COOH) groups;
- a residue of formula $-\text{CH}_2-\text{CH}_2-\text{Z}-(\text{CH}_2-\text{CH}_2\text{O})_n\text{R}''$ wherein R'' is H or C_1 - C_5 -alkyl, n is an integer from 0 to 5 and Z is oxygen or sulfur;
- a residue of formula $-(\text{CH}_2)_n-\text{NRaRb}$ wherein n is an integer from 0 to 5 and each Ra and Rb, which may be the same or different, are C_1 - C_6 -alkyl, C_1 - C_6 -alkenyl or,
- 20 alternatively, Ra and Rb, together with the nitrogen atom to which they are bound, form a heterocycle from 3 to 7 members of formula (II)



- 25 - wherein W represents a single bond, CH_2 , O, S or N- Rc , wherein Rc is H, C_1 - C_6 -alkyl or C_1 - C_6 -alkylphenyl;
- a residue OR'' wherein R'' has the same meanings as R' hereinbefore defined;

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- a residue of formula SO_2Rd wherein Rd is $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-cycloalkyl}$, $\text{C}_1\text{-C}_6\text{-alkenyl}$;

for use as inhibitors of IL-8 induced human PMNs chemotaxis.

The aromatic ring in the A group may be optionally substituted with further groups such as $\text{C}_1\text{-C}_5\text{-alkyl}$ or a halogen group.

The term "substituted" in the above definition means substituted with a group selected from $\text{C}_1\text{-C}_5\text{-alkyl}$, halogen, hydroxy, $\text{C}_1\text{-C}_5\text{-alkoxy}$, amino, $\text{C}_1\text{-C}_5\text{-alkylamino}$, nitro, or a cyano group.

Preferred A groups in compounds of formula (I) are aromatic or heteroaromatic rings selected from benzene, naphthalene, pyridine, pyrimidine, pyrrole, imidazole, furane, thiophene, indole and 7-aza-indole.

Preferred R groups in compounds of formula (I) are 3'-benzoyl, 3'-(4-chloro-benzoyl), 3'-(4-methyl-benzoyl), 3'-acetyl, 3'-propionyl, 3'-isobutanoyl, 3'-ethyl, 3'-isopropyl, 4'-isobutyl, 4'-trifluoromethanesulphonyloxy, 4'-benzenesulphonyloxy, 4'-trifluoromethanesulphonylamino, 4'-benzenesulphonylamino, 4'-benzenesulphonylmethyl, 4'-acetyloxy, 4'-propionyloxy, 4'-benzoyloxy, 4'-acetylamino, 4'-propionylamino, 4'-benzoylamino.

Preferred compounds of formula (I) are those wherein the group YR' is OH; preferred R' groups when Y is NH are:

- the amino acid residue of glycine, β -alanine, γ -aminobutyric acid or residues of an L- α -amino acid selected in the group of L-alanine, valine, leucine, isoleucine, nor-leucine, phenylalanine, S-methylcysteine, methionine;

- a residue of formula $-\text{CH}_2\text{-CH}_2\text{-O-(CH}_2\text{-CH}_2\text{O)R}''$ wherein R'' is H or $\text{C}_1\text{-C}_5\text{-alkyl}$;

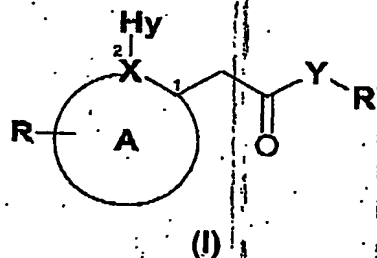
- a residue of formula $-(\text{CH}_2)_n\text{-NRaRb}$ wherein n is an integer from 2 to three, more preferably 3 and the group NRaRb is N,N-dimethylamine, N,N-diethylamine, 1-piperidyl, 4-morpholyl, 1-pyrrolidyl, 1-piperazinyl, 1-(4-methyl)piperazinyl;

- a residue OR' wherein R' is H, methyl, carboxymethyl or methylcarboxymethyl;

- a residue of formula SO_2Rd wherein Rd is methyl, ethyl or isopropyl.

The present invention further provides novel 2-arylacetic acids and derivatives of formula (I),

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and pharmaceutically acceptable salts thereof,
wherein:

A includes the X atom and represents a 5-6 membered aromatic or heteroaromatic ring optionally including a heteroatom, or a further heteroatom when X is N, selected from N (nitrogen), O (oxygen), S (sulfur); the 5-6 membered aromatic or heteroaromatic ring is optionally fused with a second ring to give bicyclic aromatic or heteroaromatic structures; labels 1 and 2 mark the relevant positions on the A ring;

the X atom is selected from N (nitrogen) and C (carbon);

R is a substituting group on the A ring selected from:

- a group in the 3 (meta) position selected from a linear or branched C₁-C₅ alkyl, C₂-C₅-alkenyl or C₂-C₅-alkynyl group, substituted or not-substituted phenyl, linear or branched C₁-C₅ hydroxyalkyl, C₂-C₅-acyl, substituted or not-substituted benzoyl;
- a group in the 4 (para) position selected from C₁-C₅ alkyl, C₂-C₅-alkenyl or C₂-C₅-alkynyl group, C₃-C₆-cycloalkyl, C₁-C₅-acyloxy, substituted or not-substituted benzoyloxy, C₁-C₅-acylamino, substituted or not-substituted benzoylamino, C₁-C₅-sulfonyloxy, substituted or not-substituted benzenesulfonyloxy, C₁-C₅-alkanesulfonylamino, substituted or not-substituted benzenesulfonylamino, C₁-C₅-alkanesulfonylmethyl, substituted or not-substituted benzenesulfonylmethyl, 2-furyl; 3-tetrahydrofuryl; 2 thiophenyl; 2-tetrahydrothiophenyl groups or a C₁-C₈-alkanoyl, cycloalkanoyl or arylalkanoyl-C₁-C₅-alkylamino group; such as acetyl-N-methyl-amino, pivaloyl-N-ethyl-amino group;

Hy is a small hydrophobic group with a steric hindrance factor ν ranging between 0.5 and 0.9 Å (where ν is the Charton steric constant for substituents), including

methyl, ethyl, chlorine, bromine, methoxy, trifluoromethyl;

13

Y is NH and R' is a residue of formula SO_2R_d wherein R_d is C_1-C_6 -alkyl, C_1-C_6 -cycloalkyl, C_1-C_6 -alkenyl.

Particularly preferred Compounds of the invention are:

- (3-benzoyl-2-methylphenyl)acetic acid
- 5 (2-chloro-3-propionylphenyl)acetic acid
- (3-isopropyl-2-methylphenyl)acetic acid
- (4-isobutyl-2-methylphenyl)acetic acid
- {2-methyl-4-[(phenylsulphonyl)amino]phenyl}acetic acid
- {2-methyl-4-[(trifluoromethanesulphonyl)amino]phenyl}acetic acid
- 10 {2-chloro-4-[(trifluoromethanesulphonyl)oxy]phenyl}acetic acid
- (5-acetyl-1-methyl-1H-pyrrol-2-yl)acetic acid
- [1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl]acetic acid
- (5-benzoyl-1-methyl-1H-pyrrol-2-yl)acetic acid
- [1-methyl-5-(4-chlorobenzoyl)-1H-pyrrol-2-yl]acetic acid
- 15 (5-isobutyryl-1-methyl-1H-pyrrol-2-yl)acetic acid
- (1-benzoyl-2-methyl-1H-pyrrol-3-yl)acetic acid
- (1-benzoyl-2-chloro-1H-pyrrol-3-yl)acetic acid
- (1-benzoyl-2-methyl-1H-indol-3-yl)acetic acid
- [1-(4-chlorobenzoyl)-2-methyl-1H-indol-3-yl]acetic acid
- 20 (1-isopropyl-2-methyl-1H-pyrrole[2,3-b]pyridin-3-yl)acetic acid
- (4-benzoyl-3-methyl-thien-2-yl)acetic acid
- (5-acetyl-4-methyl-pyridin-3-yl)acetic acid
- (5-benzoyl-4-methyl-pyridin-3-yl)acetic acid
- (4-acetyl-3-methyl-pyridin-2-yl)acetic acid
- 25 (4-benzoyl-3-methyl-pyridin-2-yl)acetic acid
- (4-acetyl-3-chloro-pyridin-2-yl)acetic acid
- (4-benzoyl-3-chloro-pyridin-2-yl)acetic acid
- (5-acetyl-4-chloro-pyridin-3-yl)acetic acid
- (5-benzoyl-4-chloro-pyridin-3-yl)acetic acid
- 30 (3-benzoyl-2-methoxyphenyl)acetic acid
- (5-acetyl-1-methyl-1H-pyrrol-2-yl)acetamide
- (5-acetyl-1-methyl-1H-pyrrol-2-yl)acetyl methanesulphonamide

- (5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-carboxymethylacetamide
 (S)(5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-(2-carboxyethyl)acetamide
 (5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-(3-dimethylaminopropyl)acetamide
 (S)(5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-(3-methoxy-2-carboxypropyl)acetamide
 5 (4-isobutyl-2-methylphenyl)acetamide
 (4-isobutyl-2-methylphenyl)acetyl methanesulphonamide
 (2-chloro-3-propionylphenyl)-N-(3-dimethylaminoethyl)acetamide
 (3-isopropyl-2-methylphenyl)-N-[3-(1-piperidiny)propyl]acetamide
 (3-benzoyl-2-methylphenyl)acetamide
 10 (1-benzoyl-2-methyl-1H-indol-3-yl)acetamide
 (1-benzoyl-2-methyl-1H-indol-3-yl)-N-(3-dimethylaminopropyl)acetamide
 [1-(4-chlorobenzoyl)-2-methyl-1H-indol-3-yl]acetamide
 [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetamide
 {2-methyl-4-[(trifluoromethanesulphonyl)amino]phenyl} acetyl methanesulphonamide
 15 {2-chloro-4-[(trifluoromethanesulphonyl)oxy]phenyl}-N-(2-hydroxyethoxyethyl)acetamide
 (1-benzoyl-2-methyl-1H-pyrrol-3-yl)-N-(2-methoxyethyl)acetamide
 (1-benzoyl-2-chloro-1H-pyrrol-3-yl)-N-[3-(1-morpholino)propyl]acetamide
 (5-isobutyryl-1-methyl-1H-pyrrol-2-yl)acetamide
 [1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl]acetyl methanesulphonamide
 20 (5-benzoyl-1-methyl-1H-pyrrol-2-yl)-N-(2-carboxymethyl)acetamide
 [1-methyl-5-(4-chlorobenzoyl)-1H-pyrrol-2-yl]-N-(2-hydroxyethoxyethyl)acetamide
 [1-methyl-5-(4-chlorobenzoyl)-1H-pyrrol-2-yl]acetamide
 {2-methyl-4-[(phenylsulphonyl)amino]phenyl}-N-(3-dimethylaminopropyl)acetamide
 (4-benzoyl-3-methyl-thien-2-yl)acetamide
 25 (5-acetyl-4-methyl-pyridin-3-yl)acetamide
 (5-acetyl-4-methyl-pyridin-3-yl)acetyl hydrossamic acid
 (3-benzoyl-2-methoxyphenyl)acetamide

Compounds of formula (I) wherein Y is NH and R' is SO₂R_d as above defined are prepared by transforming a compound of formula (I) wherein YR' is OH in a reactive
 30 intermediate such as an acylhalide, preferably an acyl chloride, or a known "active ester", preferably an ester with hydroxybenzotriazole, and reacting with a compound of formula NH₂SO₂R_d in presence of a suitable base, preferably potassium tert-butoxide.

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The compounds of the invention, despite of the lack of the methyl group on the propionic chain, are potent and selective inhibitors of the human PMNs chemotaxis induced by IL-8.

As above discussed, molecules lacking the above methyl group on the chiral carbon atom of the propionic chain have been generally found inactive in the IL-8 induced chemotaxis assay, owing to the key role of the methyl group in mapping the HYDROPHOBIC ALIPHATIC feature of the pharmacophore.

The general superimposition mode of the compounds of the invention to the pharmacophore hypothesis described above and outlined in Figure 1, is illustrated in Figures 3 and 4.

Figure 3 illustrates superimposition of the following compounds belonging to the class of arylacetic derivatives: (2-methyl-4-isobutylphenyl)acetic acid; (2-methyl-4-isobutylphenyl)acetyl methanesulphonamide; (2-methyl-4-isobutylphenyl)acetamide.

Figure 4 illustrates superimposition of the following compounds belonging to the class of arylacetic derivatives: (5-benzoyl-1-methyl-1H-pyrrol-2-yl)acetic acid; (1-benzoyl-2-methyl-1H-indol-3-yl)acetyl methanesulphonamide; (2-chloro-3-benzoylphenyl)acetamide.

The compounds of the invention derive their strong biological activity from the unexpected property of the Hydrophobic group (Hy) in the 2 position (Formula I) to correctly match the HYDROPHOBIC ALIPHATIC feature of the pharmacophore model represented by the solid spheres in Figures 3 and 4. A general pharmacophore superimposition mode is observed indeed for the compounds of Formula (I). The Hydrophobic group (Hy) of the retrieved ligands which partially or fully map the hypothesis invariably matches the HYDROPHOBIC ALIPHATIC feature (solid sphere, Figure 3). Furthermore, the compounds of Formula I show the required conformational arrangement of the functional groups in order to fully or partially map the other points of the pharmacophore hypothesis in a low energy conformation.

The compounds of the invention have the great advantage of lacking the chiral carbon atom with respect to the known IL-8 inhibitors belonging to the family of 2-arylpropionic acids and derivatives. The process of manufacture and purification of the known 2-arylpropionic acids and derivatives requires indeed the development of complicated enantioselective conditions or the introduction of a step of optical resolution with the consequential undesired impact on the costs of the active principle.

The compounds of the invention of formula I are generally isolated in the form of their addition salts with both organic and inorganic pharmaceutically acceptable acids and bases. Examples of such acids are selected from chloridric acid, sulfuric acid, phosphoric acid, metansulfonic acid, fumaric acid, citric acid.

5 Examples of such bases are selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, (D,L)-Lysine, L-Lysine, tromethamine.

The compounds of the invention of formula I were evaluated *in vitro* for their ability to inhibit chemotaxis of polymorphonucleate leukocytes (hereinafter referred to as PMNs) and monocytes induced by the fractions of IL-8 and GRO- α . For this purpose, in order to
10 isolate the PMNs from heparinized human blood, taken from healthy adult volunteers, mononucleates were removed by means of sedimentation on dextran (according to the procedure disclosed by W.J. Ming *et al.*, J. Immunol., 138, 1469, 1987) and red blood cells by a hypotonic solution. The cell viability was calculated by exclusion with Trypan blue, whilst the ratio of the circulating polymorphonucleates was estimated on the
15 cytocentrifugate after staining with Diff Quick.

Human recombinant IL-8 (Pepro Tech) was used as stimulating agents in the chemotaxis experiments, giving practically identical results: the lyophilized protein was dissolved in a volume of HBSS containing 0.2% bovin serum albumin (BSA) so thus to obtain a stock solution having a concentration of 10^{-5} M to be diluted in HBSS to a concentration of 10^{-9}
20 M, for the chemotaxis assays.

During the chemotaxis assay (according to W. Falket *et al.*, J. Immunol. Methods, 33, 239, 1980) PVP-free filters with a porosity of 5 μ m and microchambers suitable for replication were used.

The compounds of the invention in formula I were evaluated at a concentration ranging
25 between 10^{-6} and 10^{-10} M; for this purpose they were added, at the same concentration, both to the lower pores and the upper pores of the microchamber. Evaluation of the ability of the compounds of the invention of formula I to inhibit IL-8-induced chemotaxis of human monocytes was carried out according to the method disclosed by Van Damme J. *et al.* (Eur. J. Immunol., 19, 2367, 1989).

30 Particularly preferred compounds of the invention are compounds of Formula I in which R groups are 3'-benzoyl, 3'-(4-chloro-benzoyl), 3'-(4-methyl-benzoyl), 3'-acetyl, 3'-propionyl, 3'-isobutanoyl, 4'-trifluoromethanesulphonyloxy, 4'-benzenesulphonyloxy, 4'-

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trifluoromethanesulphonylamino, 4'-benzenesulphonylamino, 4'-benzenesulphonylmethyl, 4'-acetyloxy, 4'-propionyloxy, 4'-benzoyloxy, 4'-acetylamino, 4'-propionylamino, 4'-benzoylamino, which show the additional property to effectively inhibit the GRO α induced PMN chemotaxis; this activity allows the therapeutical use of these compounds in IL-8 related pathologies where the CXCR2 pathway is involved specifically or in conjunction with the CXCR1 signalling.

The dual inhibitors of the IL-8 and GRO- α induced biological activities are strongly preferred in view of the therapeutical applications of interest; but the described compounds selectively acting on CXCR1 IL-8 receptor or CXCR2 GRO- α /IL-8 receptor can find useful therapeutical applications in the management of specific pathologies as below described.

The biological activity of compounds showing high potency either as inhibitors of IL-8 induced PMN chemotaxis (CXCR1) or as dual inhibitors of IL-8 and GRO- α induced PMN chemotaxis (CXCR1/CXCR2) is reported in Table 1.

TABLE 1

Biological activity data on CXCR1 and CXCR2 receptors (% of inhibition)		
Compound	IL-8 ($c=10^{-8}$ M)	GRO- α ($c=10^{-8}$ M)
(5-isobutyryl-1-methyl-1H-pyrrol-2-yl)acetic acid	58 \pm 11	65 \pm 11
(5-acetyl-1-methyl-1H-pyrrol-2-yl)acetic acid	60 \pm 7	65 \pm 5
(5-acetyl-1-methyl-1H-pyrrol-2-yl)acetamide	54 \pm 10	44 \pm 9
(5-acetyl-1-methyl-1H-pyrrol-2-yl)acetyl methanesulfonamide	50 \pm 10	46 \pm 14
(4-isobutyl-2-methylphenyl)acetic acid	60 \pm 10	4 \pm 8
(3-isopropyl-2-methylphenyl)acetic acid	62 \pm 8	5 \pm 10
(4-isobutyl-2-methylphenyl)acetyl methanesulfonamide	67 \pm 14	0 \pm 10
(2-chloro-3-propionylphenyl)acetic acid	67 \pm 14	27 \pm 8
{2-methyl-4-[(trifluoromethanesulphonyl)amino]phenyl}acetyl methanesulphonamide	60 \pm 7	52 \pm 5

All the compounds of the invention demonstrated a high degree of selectivity towards the inhibition of the IL-8 induced chemotaxis compared to the chemotaxis induced by C51 (10^{-9} M) or f-MLP (10^{-8} M).

The compounds of formula (I) were found to be totally ineffective as inhibitors of cyclooxygenase (COX) enzymes. In most cases, the compounds of formula (I) do not interfere with the production of PGE₂ induced in murine macrophages by lipopolysaccharides stimulation (LPS, 1 µg/mL) at a concentration ranging between 10⁻⁵ and 10⁻⁷ M. Inhibition of the production of PGE₂ which may be recorded, is mostly at the limit of statistical significance, and more often is below 15-20% of the basal value. The reduced effectiveness in the inhibition of the COX constitutes an advantage for the therapeutical application of compounds of the invention in as much as the inhibition of prostaglandin synthesis constitutes a stimulus for the macrophage cells to amplify synthesis of TNF-α (induced by LPS or hydrogen peroxide) that is an important mediator of the neutrophilic activation and stimulus for the production of the cytokine Interleukin-8.

In view of the experimental evidence discussed above and of the role performed by Interleukin-8 (IL-8) and congenetics thereof in the processes that involve the activation and the infiltration of neutrophils, the compounds of the invention are particularly useful in the treatment of a disease such as psoriasis (R. J. Nicholoff et al., *Am. J. Pathol.*, 138, 129, 1991). Further diseases which can be treated with the compounds of the present invention are intestinal chronic inflammatory pathologies such as ulcerative colitis (Y. R. Mahida et al., *Clin. Sci.*, 82, 273, 1992) and melanoma; chronic obstructive pulmonary disease (COPD), bullous pemphigoid, rheumatoid arthritis (M. Selz et al., *J. Clin. Invest.*, 87, 463, 1981), idiopathic fibrosis (E. J. Miller, previously cited, and P. C. Carré et al., *J. Clin. Invest.*, 88, 1882, 1991), glomerulonephritis (T. Wada et al., *J. Exp. Med.*, 180, 1135, 1994) and in the prevention and treatment of damages caused by ischemia and reperfusion.

Inhibitors of CXCR1 and CXCR2 activation find useful applications, as above detailed, particularly in treatment of chronic inflammatory pathologies (e.g. psoriasis) in which the activation of both IL-8 receptors is supposed to play a crucial pathophysiological role in the development of the disease.

In fact, activation of CXCR1 is known to be essential in IL-8-mediated PMN chemotaxis (Hammond M et al, *J Immunol*, 155, 1428, 1995). On the other hand, activation of CXCR2 activation is supposed to be essential in IL-8-mediated epidermal cell proliferation and angiogenesis of psoriatic patients (Kulke R et al., *J Invest Dermatol*, 110, 90, 1998).

In addition, CXCR2 selective antagonists find particularly useful therapeutic applications in the management of important pulmonary diseases like chronic obstructive pulmonary

disease COPD (D. WP Hay and H.M. Sarau., Current Opinion in Pharmacology 2001, 1:242-247).

It is therefore a further object of the present invention to provide compounds for use in the treatment of psoriasis, ulcerative colitis, melanoma, chronic obstructive pulmonary disease (COPD), bullous pemphigoid, rheumatoid arthritis, idiopathic fibrosis, glomerulonephritis and in the prevention and treatment of damages caused by ischemia and reperfusion, as well as the use of such compounds in the preparation of a medicament for the treatment of diseases as described above. Pharmaceutical compositions comprising a compound of the invention and a suitable carrier thereof, are also within the scope of the present invention.

The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may, in fact, be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

When employed as pharmaceuticals, the arylacetic acids of this invention and their derivatives are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of the invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular and intranasal. Depending on the intended route of delivery, the compounds are preferably formulated as either injectable or oral compositions. The compositions for oral

administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the acetic acid compound or its derivative usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Liquid forms, including the injectable compositions described herebelow, are always stored in the absence of light, so as to avoid any catalytic effect of light, such as hydroperoxide or peroxide formation. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As above mentioned, the arylacetic acid derivative of formula I in such compositions is typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like. The mean daily dosage will depend upon various factors, such as the seriousness of the disease and the conditions of the patient (age, sex and weight). The dose will generally vary from 1 mg or a few mg up to 1500 mg of the compounds of formula (I) per day, optionally divided into multiple administrations. Higher

dosages may be administered also thanks to the low toxicity of the compounds of the invention over long periods of time.

The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 8 of "Remington's Pharmaceutical Sciences Handbook", 18th Edition, 1990, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

The compounds of the invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can also be found in the incorporated materials in the Remington's Handbook as above.

The present invention shall be illustrated by means of the following examples which are not construed to be viewed as limiting the scope of the invention.

Abbreviations: THF: tetrahydrofuran; DMF: dimethylformamide; AcOEt: ethyl acetate, HOBZ: 1-hydroxybenzotriazol, DCC: dicyclohexylcarbodiimide.

Materials and methods

Synthesis of arylacetic acids

Example 1

(3-benzoyl-2-methylphenyl)acetic acid

Starting from the commercial reagent 2-hydroxy benzophenone and following the experimental procedure described in Italian Patent 1,283,649, 1-[(2'-hydroxy-3'-benzoyl)phenyl]prop-2-ene has been synthesised in good yield (>75%).

To a cooled (T = -15°C) solution of 1-[(2'-hydroxy-3'-benzoyl)phenyl]prop-2-ene (33 mmol) in dry CH₂Cl₂ (70 ml) N,N-diisopropylethylamine (59.7 mmol) is added and the resulting solution is left stirring for 30' at T = -15°C. Then trifluoromethanesulfonic anhydride (40.16 mmol) is dropped into the solution and at the end of the adding the mixture is left stirring for 1 h. The mixture is quenched with 2N HCl (100 mL) and the two phases are separated and debated; the organic one is washed again with 2N HCl (100 mL), with water (2 x 100 mL) and with a saturated solution of NaCl (2 x 70 ml), dried on Na₂SO₄ and evaporated under reduced pressure to give 1-[(2-trifluoromethanesulfonyloxy-3-benzoyl)phenyl]prop-2-ene (31.3 mmol) as an oily crude pure enough to be used in the following step.

To a solution of 1-[(2-trifluoromethanesulfonyloxy-3-benzoyl)phenyl]prop-2-ene (30 mmol) in CH_2Cl_2 (90 ml) water (90 mL), acetic acid (18.2 mL) and Aliquat (1.46 mmol) are added. KMnO_4 (103 mmol) is added portionwise in 90. At the end of the additions the mixture is left under stirring overnight. A 10% solution of sodium metabisulfite is added dropwise until complete bleaching of the solution. The two phases are debated and separated and the organic one is washed back with a saturated solution of NaCl (2 x 50 ml), dried on Na_2SO_4 and evaporated under reduced pressure to give an oily crude that, after flash chromatography, gives 1-[(2-trifluoromethanesulfonyloxy-3-benzoyl)phenyl]acetic acid (15 mmol) as pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3): δ 7.85 (m, 2H); 7.68 (m, 2H); 7.45 (m, 4H); 3.90 (s, 2H); 2.20 (bs, 1H, COOH).

1-[(2-trifluoromethanesulfonyloxy-3-benzoyl)phenyl]acetic acid (10.3 mmol) is dissolved in methyl alcohol (30 mL) and 96% H_2SO_4 (0.2 mL) is added. After stirring overnight at room temperature, the solvent is evaporated under reduced pressure and the crude is diluted with CH_2Cl_2 (50 ml) and washed with water (3 x 50mL), dried on Na_2SO_4 and evaporated under reduced pressure to give 1-[(2-trifluoromethanesulfonyloxy-3-benzoyl)phenyl]acetic acid methyl ester as yellow oil (9.2 mmol).

$^1\text{H-NMR}$ (CDCl_3): δ 7.80 (m, 2H); 7.65 (m, 2H); 7.45 (m, 4H); 3.90 (s, 2H); 3.72 (s, 3H).

Starting from 1-[(2-trifluoromethanesulfonyloxy-3-benzoyl)phenyl]acetic acid methyl ester, 2-methyl derivative has been prepared by means of reacting said triflate with organostannanes according the methods described by Mitchell T. N., Synthesis, 803, 1992 and Ritter K., Synthesis, 735, 1993.

The acid has been synthesized starting from 1-[(2-trifluoromethanesulfonyloxy-3-benzoyl)phenyl]acetic acid methyl ester (7.5 mmol) which has been dissolved in dry N-methyl-2-pyrrolidone (25 ml); to the mixture anhydrous LiCl (22.5 mmol), triphenylarsine (0.3 mmol) and dipalladiumtribenzylidenacetone (0.14 mmol Pd) have been added. After 5' at r.t. tetramethyltin (8.4 mmol) is added and the solution is stirred for 3h at $T=60^\circ\text{C}$. After cooling the solution to r.t., the mixture is diluted with n-hexane and a saturated solution of KF is added; after filtration and separation of the phases, the organic phase is dried over Na_2SO_4 and evaporated under vacuum. The purification of the residue by means of flash

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chromatography gives (3-benzoyl-2-methylphenyl)acetic acid methyl ester. (Ritter K., Synthesis, 735, 1993 and Mitchell T. N., Synthesis, 803, 1992).

1N NaOH (5 ml) was added to a solution of the ester in 1,4-dioxane (5 ml) and the solution is stirred at room temperature overnight. After solvent evaporation the mixture is acidified to pH=2 with 2N HCl until complete precipitation of the product, which is isolated as a white solid by filtration.

¹H-NMR (CDCl₃): δ 10.50 (bs, 1H, COOH); 7.80 (m, 2H); 7.65 (m, 2H); 7.45 (m, 4H); 3.45 (s, 2H); 2.25 (s, 3H).

Example 2

(3-isopropyl-2-methylphenyl)acetic acid

According to the procedure described in Italian Patent 283,649 and starting from the commercial reagent 2'-hydroxyacetophenone, the intermediate 1-[(2-trifluoromethanesulfonyloxy-3-isopropyl)phenyl]acetic acid methyl ester has been synthesised.

¹H-NMR (CDCl₃): δ 7.55-7.40 (m, 3H); 3.85 (s, 2H); 3.70 (s, 3H); 2.45 (s, 3H).

A solution of 1-[(2-trifluoromethanesulfonyloxy-3-isopropyl)phenyl]acetic acid methyl ester (7.5 mmol) in dry THF (5 mL) is slowly dropped into a mixture of methyltriphenylphosphonium bromide (7.5 mmol) and n-BuLi (7.5 mmol; 1.6 M in n-hexane) in dry THF (10 mL). At the end of the additions the mixture is left under stirring overnight at room temperature. A 10% solution of sodium metabisulfite (20 mL) is added dropwise and the two phases are debated and separated; the organic phase is dried over Na₂SO₄ and evaporated under vacuum. The purification of the residue by means of flash chromatography gives 1-[(2-trifluoromethanesulfonyloxy-3-isopropen-2'-yl)phenyl]acetic acid methyl ester as colourless oil (5.28 mmol).

¹H-NMR (CDCl₃): δ 7.55-7.40 (m, 3H); 5.50 (s, 2H); 3.80 (s, 2H); 3.74 (s, 3H); 1.63 (s, 3H).

The reduction of 1-[(2-trifluoromethanesulfonyloxy-3-isopropen-2'-yl)phenyl]acetic acid methyl ester has been carried out by hydrogenolysis with Pd/C in absolute ethyl alcohol to give after catalyst filtration and mother liquors evaporation under reduced pressure, pure (3-isopropyl-2-methylphenyl)acetic acid methyl ester as pale yellow oil (5 mmol).

¹H-NMR (CDCl₃): δ 7.52-7.45 (m, 3H); 3.82 (s, 2H); 3.70 (s, 3H); 2.65 (m, 1H); 1.25 (d, 6H, J=8Hz).

Following the procedure described for Example 1 and starting from (3-isopropyl-2-methylphenyl)acetic acid methyl ester (7.0 mmol) pure (3-isopropyl-2-methylphenyl)acetic acid has been synthesised (5.45 mmol).

¹H-NMR (CDCl₃): δ 11.2 (bs, 1H, COOH); 7.35-7.20 (m, 3H); 3.80 (s, 2H); 2.55 (m, 1H); 2.22 (s, 3H); 1.28 (d, 6H, J=8Hz).

Example 3

(2-chloro-3-propionylphenyl)acetic acid

10 According to the procedure described in Italian Patent 1,283,649 and starting from the commercial reagent 2'-hydroxypropiophenone, the intermediate 1-[(2-hydroxy-3-propionyl)phenyl]prop-2-ene has been synthesised.

By treatment of the compound by PhPCl₂, according to the procedure described by Bay et al., J. Org. Chem., Vol. 32, 3415, 1990, 1-[(2-chloro-3-propionyl)phenyl]prop-2-ene (5.1 mmol): Following the procedure for the double bond oxidation described in the Example 1, pure (2-chloro-3-propionylphenyl)acetic acid has been synthesised (4.15 mmol).

¹H-NMR (CDCl₃): δ 10.18 (bs, 1H, COOH); 7.40-7.24 (m, 3H); 3.65 (s, 2H); 2.75 (q, 2H, J₁=8Hz, J₂=3Hz); 1.15 (t, 3H, J=8Hz).

20 Example 4

(4-isobutyl-2-methylphenyl)acetic acid

The compound has been prepared by double Stille reaction on the starting reagent 2-(2-acetoxy-4-perfluorbutanesulfonyloxy)phenylacetic acid methyl ester (prepared according known procedures) following the same experimental procedure used for the synthesis of analogous arylpropionic acids and described in WO 01/58852 A2.

¹H-NMR (CDCl₃): δ 7.22 (d, 1H, J=8Hz); 7.05 (d, 1H, J=8Hz); 6.92 (s, 1H); 3.50 (s, 2H); 2.40 (d, 2H, J=7Hz); 2.20 (s, 3H); 1.95 (m, 1H); 0.95 (d, 6H, J=7Hz).

Example 5

{2-methyl-4-[(phenylsulphonyl)amino]phenyl}acetic acid

30 The synthesis of the compound has been carried out as follows:
the commercial reagent 2-hydroxy-4-nitrobenzoic acid has been transformed into 2-hydroxy-4-nitroacetophenone by the Meldrum's acid pathway to methyl ketones, according

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to the experimental procedure described by Hase T.A. et al., Synthetic Communications, 10(3), 221-224, 1980. The treatment of 2-hydroxy-4-nitroacetophenone with trifluoromethanesulfonic anhydride has given the 2-trifluoromethanesulfonyloxy derivative that, by Stille reaction according the experimental procedure described in Example 1, has
5 afforded the 2-methyl-4-nitroacetophenone.

Starting from 2-methyl-4-nitroacetophenone and following the procedure described in Italian Patent 1,283,649 the 2-methyl-4-nitro phenylacetic acid methyl ester has been synthesised.

¹H-NMR (CDCl₃): δ 7.50-7.42 (m, 3H); 3.80 (s, 2H); 3.64 (s, 3H); 2.25 (s, 3H).

10 To a solution of 2-methyl-4-nitro phenylacetic acid methyl ester (10 mmol) in dry THF (20 mL) and methyl alcohol (20 mL), ammonium formate (0.1 mol) and 10% Pd/C (0.5 g) have been added and the resulting mixture has been left stirring for 3 h until complete disappearance of the starting reagent. The catalyst has been filtered off and the filtrate evaporated under vacuum to give 2-methyl-4-amino phenylacetic acid methyl ester
15 as a waxy solid (9.22 mmol).

¹H-NMR (CDCl₃): δ 7.51 (m, 1H); 7.40 (m, 1H); 7.15 (m, 1H); 5.00 (bs, 2H, NH₂); 3.82 (s, 2H); 3.65 (s, 3H); 2.20 (s, 3H).

To a solution of 2-methyl-4-amino phenylacetic acid methyl ester (5.3 mmol) in acetone (10 mL) dry pyridine (7.95 mmol) and phenylsulfonyl chloride (6.36 mmol) have
20 been added and the resulting solution has been left stirring overnight at room temperature. Acetone has been evaporated and the residue diluted with CCl₄ (15 mL), washed with 1N HCl (2 x 10 mL), water (3 x 20 mL), dried over Na₂SO₄ and evaporated under vacuum to give {2-methyl-4-[(phenylsulphonyl)amino]phenyl}acetic acid methyl ester as colourless oil (5.0 mmol) pure to be used in the following reaction. Following the procedure described
25 for Example 1 and starting from the methyl ester (5.0 mmol) pure {2-methyl-4-[(phenylsulphonyl)amino]phenyl}acetic acid has been synthesised (4.75 mmol).

¹H-NMR (CDCl₃): δ 9.40 (s, 1H, SO₂NH); 7.73 (m, 2H); 7.42 (m, 3H); 7.50 (m, 1H); 7.45 (m, 1H); 7.15 (m, 1H); 3.82 (s, 2H); 2.21 (s, 3H).

30 According to the same experimental procedure and using as reagent trifluoromethanesulfonic anhydride, the following compound has been synthesised:

Example 6

{2-methyl-4-[(trifluoromethanesulfonyl)amino]phenyl}acetic acid

¹H-NMR (CDCl₃): δ 9.35 (s, 1H, SO₂NH); 7.54 (m, 1H); 7.40 (m, 1H); 7.20 (m, 1H); 3.80 (s, 2H); 2.25 (s, 3H).

Example 7{2-chloro-4-[(trifluoromethanesulfonyl)oxy]phenyl}acetic acid

Starting from the intermediate 2-hydroxy-4-nitroacetophenone (described in the Example 5), the synthesis of the 2-chloro derivative has been carried out following the experimental procedure described by Bay et al., J. Org. Chem., Vol. 32, 3115, 1990. The intermediate 2-chloro-4-nitroacetophenone has been transformed into the intermediate 2-chloro-4-amino phenylacetic acid methyl ester according the same procedure described in Example 5.

¹H-NMR (CDCl₃): δ 7.55-7.45 (m, 3H); 3.85 (s, 2H); 3.60 (s, 3H).

After treatment of 2-chloro-4-amino phenylacetic acid methyl ester with sodium nitrite in acidic conditions and following replacement of the diazonium ion with the hydroxyl group as described in Organic Synthesis, III, 453, (2-chloro-4-hydroxyphenyl)acetic acid has been obtained as white solid.

¹H-NMR (CDCl₃): δ 7.74-7.60 (m, 3H); 6.35 (bs, 1H, OH); 3.85 (s, 2H).

A mixture of the above described (2-chloro-4-hydroxyphenyl)acetic acid (2 mmol), trifluoromethanesulfonic anhydride (4 mmol) in dry pyridine (1 mL) has been warmed at T=60°C for 24 hours. After cooling at room temperature the reaction mixture has been poured into 1 N HCl (5 mL) and the aqueous solution extracted with CH₂Cl₂ (3 x 10 mL). The collected organic extracts have been washed back with 1N NaOH (2 x 10 mL), dried over Na₂SO₄ and evaporated under reduced pressure to give a crude residue. The crystallisation in isopropyl ether of the crude has given the pure {2-chloro-4-[(trifluoromethanesulfonyl)oxy]phenyl}acetic acid as white solid (1.25 mmol).

¹H-NMR (CDCl₃): δ 7.70-7.62 (m, 3H); 3.85 (s, 2H).

Example 8(5-benzoyl-1-methyl-1H-pyrrol-2-yl)acetic acid

The compound has been synthesised starting from the commercial reagents 1-methyl-2-pyrrolicarboxaldehyde and benzoyl chloride and following the experimental procedure described in Di Santo R. et al. Synth. Comm., 25(6), 787-793 (1995).

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¹H-NMR (CDCl₃): δ 7.85 (m, 2H); 7.52 (m, 1H); 7.45 (m, 2H); 6.70 (s, 1H), 6.15 (s, 1H); 3.97 (s, 3H); 3.75 (s, 2H); 3.0 (bs, 1H, COOH).

According the same experimental procedures and starting from the related commercial acyl chlorides, the following compounds have been prepared:

Example 9[1-methyl-5-(4-chlorobenzoyl)-1H-pyrrol-2-yl]acetic acid

¹H-NMR (CDCl₃): δ 7.82 (d, 2H, J=8Hz); 7.58 (d, 2H, J=8Hz); 7.20 (s, 1H), 6.68 (s, 1H); 3.75 (s, 2H); 3.70 (s, 3H).

Example 10[1-methyl-5-[(4-methylbenzoyl)-1H-pyrrol-2-yl]acetic acid

¹H-NMR (CDCl₃): δ 7.80 (d, 2H, J=8Hz); 7.55 (d, 2H, J=8Hz); 7.18 (s, 1H), 6.72 (s, 1H); 3.75 (s, 2H); 3.70 (s, 3H); 2.35 (s, 3H).

Example 11(5-acetyl-1-methyl-1H-pyrrol-2-yl)acetic acid

¹H-NMR (CDCl₃): δ 6.90 (d, 1H, J=3Hz); 6.05 (d, 1H, J=3Hz); 3.80 (s, 3H), 3.62 (s, 2H); 2.32 (s, 3H).

Example 12(5-isobutyryl-1-methyl-1H-pyrrol-2-yl)acetic acid

¹H-NMR (CDCl₃): δ 7.55 (s, 1H); 6.32 (s, 1H); 3.65 (s, 2H); 3.52 (s, 3H); 3.15 (m, 1H); 1.05 (d, 6H, J=7Hz).

Example 13(1-benzoyl-2-methyl-1H-pyrrol-3-yl)acetic acid

The intermediate (2-methyl-1H-pyrrol-3-yl)acetic acid ethyl ester has been synthesised as described in Bertschy H., et al., Angew. Chem. Int. Ed. Engl. 29(7), 777-778 (1990).

The following N-benzoylation and ester hydrolysis according well known procedures (NaH/ benzoyl chloride) give the desired product.

¹H-NMR (CDCl₃): δ 8.15 (m, 2H); 7.60 (m, 1H); 7.45 (m, 2H); 6.95 (d, 1H, J=3Hz); 6.32 (d, 1H, J=3Hz); 4.50 (bs, 1H, COOH); 3.85 (s, 2H); 2.35 (s, 3H).

Example 14(1-benzoyl-2-chloro-1H-pyrrol-3-yl)acetic acid

The product has been synthesised by a multistep synthesis according well known literature procedures. The condensation of the commercial reagent diethyl malonate with bromoacetaldehyde dimethyl acetal and the acetal hydrolysis allows to obtain the intermediate aldehyde which, after treatment with gaseous ammonia and dehydration of the not isolated intermediate enamine, gives the pure intermediate 2-hydroxypyrrole-3-acetic acid ethyl ester.

$^1\text{H-NMR}$ (CDCl_3): δ 10.35 (bs, 1H, NH); 7.21 (d, 1H, $J=3\text{Hz}$); 7.05 (bs, 1H, OH); 6.35 (d, 1H, $J=3\text{Hz}$); 4.12 (q, 2H, $J=7\text{Hz}$); 3.45 (s, 2H); 1.31 (t, 3H, $J=7\text{Hz}$).

The pyrrole intermediate, after treatment with PCl_5 , gives the 2-chloro derivative which, after ester hydrolysis in usual conditions ($\text{NaOH}/\text{CH}_3\text{OH}$) and N-benzoylation, affords the pure compound (1-benzoyl-2-chloro-1H-pyrrol-3-yl)acetic acid as white solid (yield 78%).

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 8.15 (m, 2H); 7.60 (m, 1H); 7.45 (m, 2H); 6.92 (d, 1H, $J=3\text{Hz}$); 6.35 (d, 1H, $J=3\text{Hz}$); 4.65 (bs, 1H, COOH); 3.82 (s, 2H).

Example 15

(1-benzoyl-2-methyl-1H-indol-3-yl)acetic acid

The commercial reagent 2-methyl-3-indoleacetic acid (3 mmol) has been treated with NaH (6.6 mmol) and benzoyl chloride (6.6 mmol) in dry THF (10 mL) according well known procedures. The usual reaction work up and crystallisation of the residue in isopropyl ether led to the pure (1-benzoyl-2-methyl-1H-indole-3-yl)acetic acid as white solid (2.25 mmol).

$^1\text{H-NMR}$ (CDCl_3): δ 7.82-7.70 (m, 3H); 7.55 (t, 2H, $J=8.5\text{ Hz}$); 6.90-6.80 (m, 2H); 6.65 (m, 2H); 3.62 (s, 2H); 3.30 (s, 3H).

Example 16

[1-(4-chlorobenzoyl)-2-methyl-1H-indol-3-yl]acetic acid

The commercial reagent 2-methyl-3-indoleacetic acid (3 mmol) has been treated with NaH (6.6 mmol) and 4-chlorobenzoyl chloride (6.6 mmol) in dry THF (10 mL) according well known procedures. The usual reaction work up and crystallisation of the residue in isopropyl ether led to the pure [1-(4-chlorobenzoyl)-2-methyl-1H-indol-3-yl]acetic acid as white solid (2.01 mmol).

$^1\text{H-NMR}$ (CDCl_3): δ 7.80-7.70 (t, 2H, $J=8.5\text{ Hz}$); 7.55 (t, 2H, $J=8.5\text{ Hz}$); 6.90 (s, 1H); 6.80 (m, 1H); 3.60 (s, 2H); 3.30 (s, 3H).

Example 17

(1-isopropyl-2-methyl-1H-pyrrole[2,3-b]pyridin-3-yl)acetic acid

The commercial reagent 1H-pyrrole[2,3-b]pyridine (3 mmol) has been treated with NaH (3.3 mmol) and isopropyl chloride (3.3 mmol) in dry THF (10 mL) according well known procedures. The usual reaction work up and purification of the residue by chromatography led to the pure 1-isopropyl-1H-pyrrole[2,3-b]pyridine as white solid (2.83 mmol).

¹H-NMR (CDCl₃): δ 7.65 (m, 1H); 7.15-7.08 (m, 2H); 7.00 (m, 1H); 6.50 (m, 1H); 3.12 (m, 1H); 1.05 (d, 6H, J=7Hz).

Following the experimental procedure described by Chi S. M. et al., Tetrahedron Letters, 41, 919-922 (2000) and starting from 1-isopropyl-1H-pyrrole[2,3-b]pyridine (2.5 mmol), (1-isopropyl-2-methyl-1H-pyrrole[2,3-b]pyridin-3-yl)ethoxy acetate has been isolated (2.0 mmol). The final oxidation by KMnO₄ in phase transfer catalysis conditions (described in Example 1) has led to the desired product (1-isopropyl-2-methyl-1H-pyrrole[2,3-b]pyridin-3-yl)acetic acid (1.85 mmol).

¹H-NMR (CDCl₃): δ 7.15 (m, 1H); 7.10 (m, 1H); 6.95 (m, 1H); 3.55 (s, 2H); 3.11 (m, 1H); 2.35 (s, 3H); 1.05 (d, 6H, J=7Hz).

Example 18(3-benzoyl-2-methoxyphenyl)acetic acid

(3-benzoyl-2-hydroxyphenyl)acetic acid methyl ester, prepared according know procedures from 2-hydroxybenzophenone, has been treated with potassium carbonate and iodomethane in acetone to give the corresponding 2-methoxy derivative that, after usual hydrolysis (NaOH/CH₃OH) has given (3-benzoyl-2-methoxyphenyl)acetic acid as white solid.

¹H-NMR (CDCl₃): δ 7.90 (d, 2H, J=7Hz); 7.62 (m, 1H); 7.50-7.40 (m, 3H); 7.35 (m, 1H); 7.15 (t, 1H, J=7Hz); 3.82 (s, 2H); 3.60 (s, 3H).

Synthesis of arylacetic amides

According to the experimental procedure described in WO 01/58852 and starting from the related acetic acid, the following compounds have been synthesised:

Example 19(5-acetyl-1-methyl-1H-pyrrol-2-yl)acetamide

¹H-NMR (CDCl₃): δ 6.92 (d, 1H, J=3Hz); 6.05 (d, 1H, J=3Hz); 5.25 (bs, 2H, CONH₂); 3.81 (s, 3H); 3.68 (s, 2H); 2.35 (s, 3H).

Example 20

30

(5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-carboxymethylacetamide

¹H-NMR (CDCl₃): δ 6.90 (d, 1H, J=3Hz); 6.05 (d, 1H, J=3Hz); 5.95 (d, 1H, J=7Hz, CONH); 4.05 (d, 2H, J=7Hz); 3.81 (s, 3H); 3.68 (s, 2H); 2.35 (s, 3H).

Example 21(S)(5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-(2-carboxyethyl)acetamide

¹H-NMR (CDCl₃): δ 6.92 (d, 1H, J=3Hz); 6.05 (d, 1H, J=3Hz); 6.00 (bs, 1H, CONH); 4.53 (q, 1H, J=7Hz); 3.81 (s, 3H); 3.68 (s, 2H); 2.35 (s, 3H); 1.55 (d, 3H, J=7Hz).

Example 22(5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-(3-dimethylaminopropyl)acetamide

¹H-NMR (CDCl₃): δ 7.75 (bs, 1H, CONH); 6.92 (d, 1H, J=3Hz); 6.28 (d, 1H, J=3Hz); 4.10 (s, 3H); 3.80 (s, 2H); 3.54 (m, 2H); 2.48 (t, 2H, J=7Hz); 2.40 (s, 3H); 2.19 (s, 6H); 1.76 (m, 2H).

Example 23(S)(5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-(3-methoxy-2-carboxypropyl)acetamide

¹H-NMR (CDCl₃): δ 7.45 (bs, 1H, CONH); 6.92 (d, 1H, J=3Hz); 6.05 (d, 1H, J=3Hz); 4.53 (q, 1H, J=7Hz); 3.81 (s, 3H); 3.68 (s, 2H); 3.20 (s, 3H); 3.15 (d, 2H, J=7Hz); 2.35 (s, 3H).

Example 24(4-isobutyl-2-methylphenyl)acetamide

¹H-NMR (CDCl₃): δ 7.20 (d, 1H, J=8Hz); 7.05 (d, 1H, J=8Hz); 6.95 (s, 1H); 5.70 (bs, 2H, CONH₂); 3.68 (s, 2H); 2.40 (d, 2H, J=7Hz); 2.22 (s, 3H); 1.95 (m, 1H); 0.95 (d, 6H, J=7Hz).

Example 25(2-chloro-3-propionylphenyl)-N-(3-dimethylaminoethyl)acetamide

¹H-NMR (CDCl₃): δ 7.50 (bs, 1H, CONH); 7.40-7.24 (m, 3H); 3.62 (s, 2H); 3.54 (m, 2H); 2.75 (q, 2H, J₁=8Hz, J₂=3Hz); 2.25 (t, 2H, J=7Hz); 2.19 (s, 6H); 1.15 (t, 3H, J=8Hz).

Example 26(3-isopropyl-2-methylphenyl)-N-[3-(1-piperidinyl)propyl]acetamide

¹H-NMR (CDCl₃): δ 7.45 (bs, 1H, CONH); 7.35-7.20 (m, 3H); 3.80 (s, 2H); 3.50 (m, 2H); 3.32 (m, 2H); 2.95 (m, 2H); 2.55 (m, 1H); 2.45 (m, 2H); 2.22 (s, 3H); 2.10 (m, 2H); 1.90 (m, 6H); 1.28 (d, 6H, J=8Hz).

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Example 27**(3-benzoyl-2-methylphenyl)acetamide**

¹H-NMR (CDCl₃): δ 7.82 (m, 2H); 7.60 (m, 2H); 7.45 (m, 4H); 5.45 (bs, 2H, CONH₂); 3.70 (s, 2H); 2.25 (s, 3H).

Example 28**(1-benzoyl-2-methyl-1H-indol-3-yl)acetamide**

¹H-NMR (CDCl₃): δ 7.82-7.70 (m, 3H); 7.55 (t, 2H, J=8.5 Hz); 6.90-6.80 (m, 2H); 6.65 (m, 2H); 5.75 (bs, 2H, CONH₂); 3.68 (s, 2H); 3.30 (s, 3H).

Example 29**(1-benzoyl-2-methyl-1H-indol-3-yl)-N-(3-dimethylaminopropyl)acetamide**

¹H-NMR (CDCl₃): δ 7.80-7.72 (m, 3H); 7.60 (bs, 1H, CONH); 7.55 (t, 2H, J=8.5 Hz); 6.90-6.80 (d, 2H, J=8Hz); 6.65 (d, 2H, J=8Hz); 3.80 (s, 2H); 3.58 (m, 2H); 3.30 (s, 3H); 2.50 (t, 2H, J=7Hz); 2.20 (s, 6H); 1.80 (m, 2H).

Example 30**[1-(4-chlorobenzoyl)-2-methyl-1H-indol-3-yl]acetamide**

¹H-NMR (CDCl₃): δ 7.80-7.70 (m, 2H, J=8.5 Hz); 7.55 (t, 2H, J=8.5 Hz); 6.92-6.80 (d, 2H, J=8Hz); 6.68 (d, 2H, J=8Hz); 5.62 (bs, 2H, CONH₂); 3.70 (s, 2H); 3.30 (s, 3H).

Example 31**[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetamide**

¹H-NMR (CDCl₃): δ 7.82-7.75 (m, 2H, J=8.5 Hz); 7.55 (m, 2H); 6.92-6.70 (m, 3H); 5.60 (bs, 2H, CONH₂); 3.82 (s, 3H); 3.66 (s, 2H); 3.30 (s, 3H).

Example 32**{2-chloro-4-[(trifluoromethanesulfonyl)oxy]phenyl}-N-(2-hydroxyethoxyethyl)acetamide**

¹H-NMR (CDCl₃): δ 7.70-7.62 (m, 3H); 5.90 (bs, 1H, CONH); 3.80 (s, 2H); 3.65 (m, 2H); 3.55-3.32 (m, 6H); 2.05 (bs, 1H, OH).

Example 33**(1-benzoyl-2-methyl-1H-pyrrol-3-yl)-N-(2-methoxyethyl)acetamide**

¹H-NMR (CDCl₃): δ 8.12 (m, 2H); 7.60 (m, 1H); 7.50 (m, 2H); 6.92 (d, 1H, J=3Hz); 6.32 (d, 1H, J=3Hz); 5.65 (bs, 1H, CONH); 3.75 (s, 2H); 3.25 (t, 2H, J=8Hz); 3.20 (s, 3H); 2.97 (m, 2H); 2.35 (s, 3H).

Example 34**(1-benzoyl-2-chloro-1H-pyrrol-3-yl)-N-[3-(1-morpholino)propyl]acetamide**

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$^1\text{H-NMR}$ (CDCl_3): δ 8.15 (m, 2H); 7.60 (m, 1H); 7.45 (m, 2H); 6.92 (d, 1H, $J=3\text{Hz}$); 6.35 (d, 1H, $J=3\text{Hz}$); 6.20 (bs, 1H, CONH); 3.78 (s, 2H); 3.25 (m, 4H); 2.98 (m, 2H); 2.45 (m, 6H); 1.80 (m, 2H).

Example 355 (5-isobutyryl-1-methyl-1H-pyrrol-2-yl)acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.50 (s, 1H); 6.35 (s, 1H); 5.85 (bs, 2H, CONH₂); 3.77 (s, 2H); 3.50 (s, 3H); 3.18 (m, 1H); 1.05 (d, 6H, $J=7\text{Hz}$).

Example 3610 (5-benzoyl-1-methyl-1H-pyrrol-2-yl)-N-(2-carboxymethyl)acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 10.53 (bs, 1H, COOH); 7.85 (m, 2H); 7.52 (m, 1H); 7.45 (m, 2H); 6.70 (s, 1H); 6.15 (s, 1H); 5.95 (d, 1H, $J=7\text{Hz}$, CONH); 4.05 (d, 2H, $J=7\text{Hz}$); 3.95 (s, 3H); 3.68 (s, 2H).

Example 3715 [1-methyl-5-(4-chlorobenzoyl)-1H-pyrrol-2-yl]-N-(2-hydroxyethoxyethyl)acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.82 (d, 2H, $J=8\text{Hz}$); 7.55 (d, 2H, $J=8\text{Hz}$); 7.40 (bs, 1H, CONH); 7.35 (s, 1H); 6.65 (s, 1H); 3.70 (s, 2H); 3.65 (s, 3H); 3.60 (m, 2H); 3.50-3.42 (m, 6H); 2.25 (bs, 1H, OH).

Example 3820 [1-methyl-5-(4-chlorobenzoyl)-1H-pyrrol-2-yl]acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.82 (d, 2H, $J=8\text{Hz}$); 7.58 (d, 2H, $J=8\text{Hz}$); 7.20 (s, 1H); 6.68 (s, 1H); 6.35 (bs, 2H, CONH₂); 3.70 (s, 3H); 3.66 (s, 2H).

Example 3925 [2-methyl-4-[(phenylsulphonyl)amino]phenyl]-N-(3-dimethylaminopropyl)acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 9.20 (s, 1H, SO₂NH); 7.75 (m, 2H); 7.65 (bs, 1H, CONH); 7.42 (m, 3H); 7.50 (m, 1H); 7.45 (m, 1H); 7.12 (m, 1H); 3.88 (s, 2H); 3.58 (m, 2H); 2.50 (t, 2H, $J=7\text{Hz}$); 2.35 (s, 6H); 2.21 (s, 3H); 1.80 (m, 2H).

Example 4030 (3-benzoyl-2-methoxyphenyl)acetamide

$^1\text{H-NMR}$ (CDCl_3): δ 7.90 (d, 2H, $J=7\text{Hz}$); 7.62 (m, 1H); 7.50-7.40 (m, 3H); 7.35 (m, 1H); 7.15 (t, 1H, $J=7\text{Hz}$); 6.55 (bs, 2H, CONH₂); 3.82 (s, 3H); 3.66 (s, 2H).

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Synthesis of arylacetic methanesulfonamides

According to the experimental procedure described in WO 00/24710 and starting from the related acetic acid, the following compounds have been synthesised:

Example 41**(5-acetyl-1-methyl-1H-pyrrol-2-yl)acetyl methanesulfonamide**

¹H-NMR (CDCl₃): δ 7.50 (bs, 1H, CONH); 6.90 (d, 1H, J=3Hz); 6.05 (d, 1H, J=3Hz); 3.80 (s, 3H); 3.58 (s, 2H); 3.22 (s, 3H); 2.32 (s, 3H).

Example 42**(4-isobutyl-2-methylphenyl)acetyl methanesulfonamide**

¹H-NMR (CDCl₃): δ 7.20 (d, 1H, J=8Hz); 7.10 (bs, 1H, CONH); 7.00 (d, 1H, J=8Hz); 6.85 (s, 1H); 3.65 (s, 2H); 3.22 (s, 3H); 2.40 (d, 2H, J=7Hz); 2.22 (s, 3H); 1.95 (m, 1H); 0.95 (d, 6H, J=7Hz).

Example 43**{2-methyl-4-[(trifluoromethanesulfonyl)amino]phenyl}acetyl methanesulfonamide**

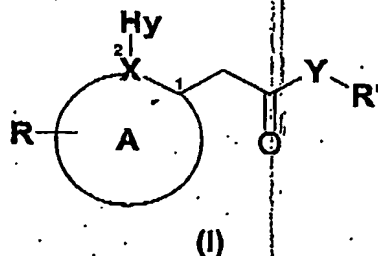
¹H-NMR (CDCl₃): δ 9.42 (bs, 1H, SO₂NH); 7.45 (bs, 1H, CONH); 7.52 (m, 1H); 7.45 (m, 1H); 7.20 (m, 1H); 3.85 (s, 2H); 3.45 (s, 3H); 2.25 (s, 3H).

Example 44**[1-methyl-5-[(4-methylbenzoyl)-1H-pyrrol-2-yl]acetyl methanesulfonamide**

¹H-NMR (CDCl₃): δ 7.80 (d, 2H, J=8Hz); 7.55 (d, 2H, J=8Hz); 7.38 (bs, 1H, CONH); 7.18 (s, 1H); 6.72 (s, 1H); 3.82 (s, 2H); 3.70 (s, 3H); 3.42 (s, 3H); 2.35 (s, 3H).

CLAIMS

1. 2-Arylacetic acid compounds and derivatives of formula (I):



and pharmaceutically acceptable salts thereof,

wherein

A includes the X atom and represents a 5-6 membered aromatic or heteroaromatic ring optionally including a heteroatom, or a further heteroatom when X is N, selected from N (nitrogen), O (oxygen), S (sulfur); the 5-6 membered aromatic or heteroaromatic ring is optionally fused with a second ring to give bicyclic aromatic or heteroaromatic structures;

labels 1 and 2 mark the relevant positions on the A ring;

the X atom is selected from N (nitrogen) and C (carbon);

R is a substituting group on the A ring selected from:

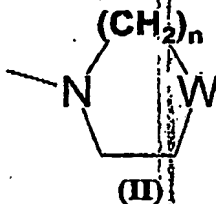
- a group in the 3 (meta) position selected from a linear or branched C₁-C₅ alkyl, C₂-C₅-alkenyl or C₂-C₅-alkynyl group, substituted or not-substituted phenyl, linear or branched C₁-C₅ hydroxyalkyl, C₂-C₅-acyl, substituted or not-substituted benzoyl;
- a group in the 4 (para) position selected from C₁-C₅ alkyl, C₂-C₅-alkenyl or C₂-C₅-alkynyl group, C₃-C₆-cycloalkyl, C₁-C₅-acyloxy, substituted or not-substituted benzoyloxy, C₁-C₅-acylamino, substituted or not-substituted benzoylamino, C₁-C₅-sulfonyloxy, substituted or not-substituted benzenesulfonyloxy, C₁-C₅-alkanesulfonylamino, substituted or not-substituted benzenesulfonylamino, C₁-C₅-alkanesulfonylmethyl, substituted or not-substituted benzenesulfonylmethyl, 2-furyl; 3-tetrahydrofuryl; 2 thiophenyl; 2-tetrahydrothiophenyl groups or a C₁-C₈-alkanoyl, cycloalkanoyl or arylalkanoyl-C₁-C₅-alkylamino group;

Hy is a small hydrophobic group with a steric hindrance factor ν ranging between 0.5 and 0.9 Å (where ν is the Charton steric constant for substituents), including methyl, ethyl, chlorine, bromine, methoxy, trifluoromethyl;

The Y group is selected from O (oxygen) and NH;
when Y is O (oxygen), R' is H (hydrogen);

When Y is NH, R' is selected from

- H, C₁-C₅-alkyl, C₁-C₅-cycloalkyl, C₁-C₅-alkenyl;
- an amino acid residue consisting of straight or branched C₁-C₆-alkyl, C₁-C₆-cycloalkyl, C₁-C₆-alkenyl, phenylalkyl substituted with one or more carboxy (COOH) groups;
- an amino acid residue consisting of straight or branched C₁-C₆-alkyl, C₁-C₆-cycloalkyl, C₁-C₆-alkenyl, phenylalkyl bearing along the chain a heteroatom selected from oxygen and sulfur and with one or more carboxy (COOH) groups;
- a residue of formula $-\text{CH}_2-\text{CH}_2-\text{Z}-(\text{CH}_2-\text{CH}_2\text{O})_n\text{R}''$ wherein R'' is H or C₁-C₅-alkyl, n is an integer from 0 to 5 and Z is oxygen or sulfur;
- a residue of formula $-(\text{CH}_2)_n-\text{NRaRb}$ wherein n is an integer from 0 to 5 and each Ra and Rb, which may be the same or different, are C₁-C₆-alkyl, C₁-C₆-alkenyl or, alternatively, Ra and Rb, together with the nitrogen atom to which they are bound, form a heterocycle from 3 to 7 members of formula (II)



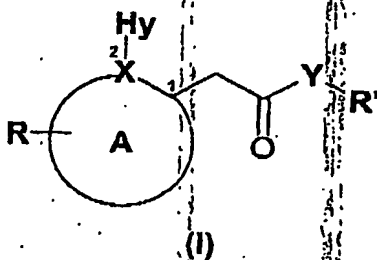
- wherein W represents a single bond, CH₂, O, S or N-Rc, wherein Rc is H, C₁-C₆-alkyl or C₁-C₆-alkylphenyl;
- a residue OR'' wherein R'' has the same meanings as R', hereinbefore defined;
- a residue of formula SO₂Rd wherein Rd is C₁-C₆-alkyl, C₁-C₆-cycloalkyl, C₁-C₆-alkenyl;

for use as inhibitors of IL-8 induced human PMNs chemotaxis.

2. Compounds according to claim 1, wherein A is benzene, naphtalene, pyridine, pyrimidine, pyrrole, imidazole, furane, thiophene, indole and 7-aza-indole.
3. Compounds according to claim 1, wherein YR' is OH.
4. Compounds according to claim 1, wherein Y is NH and R' is:

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- the amino acid residue of glycine, β -alanine, γ -aminobutyric acid or residues of an L- α -amino acid selected in the group of L-alanine, valine, leucine, isoleucine, norleucine, phenylalanine, S-methylcysteine, methionine;
 - a residue of formula $-\text{CH}_2-\text{CH}_2-\text{O}-(\text{CH}_2-\text{CH}_2\text{O})\text{R}''$ wherein R'' is H or C_1-C_5 -alkyl;
 - a residue of formula $-(\text{CH}_2)_n-\text{NRaRb}$ wherein n is an integer from 2 to three, more preferably 3 and the group NRaRb is N,N-dimethylamine, N,N-diethylamine, 1-piperidyl, 4-morpholyl, 1-pyrrolidyl, 1-piperazinyl, 1-(4-methyl)piperazinyl;
 - a residue OR' wherein R' is H, methyl, carboxymethyl or methylcarboxymethyl;
 - a residue of formula SO_2Rd wherein Rd is methyl, ethyl or isopropyl.
5. Compounds according to claim 1, wherein R is 3'-benzoyl, 3'-(4-chloro-benzoyl), 3'-(4-methyl-benzoyl), 3'-acetyl, 3'-propionyl, 3'-isobutanoyl, 3'-ethyl, 3'-isopropyl, 4'-isobutyl, 4'-trifluoromethanesulphonyloxy, 4'-benzenesulphonyloxy, 4'-trifluoromethanesulphonylamino, 4'-benzenesulphonylamino, 4'-benzenesulphonylmethyl, 4'-acetyloxy, 4'-propionyloxy, 4'-benzoyloxy, 4'-acetylamino, 4'-propionylamino, 4'-benzoylamino.
6. 2-Arylacetic acid compounds and derivatives of formula (I)



and pharmaceutically acceptable salts thereof,

wherein :

A includes the X atom and represents a 5-6 membered aromatic or heteroaromatic ring optionally including a heteroatom, or a further heteroatom when X is N, selected from N (nitrogen), O (oxygen), S (sulfur); the 5-6 membered aromatic or heteroaromatic ring is optionally fused with a second ring to give bicyclic aromatic or heteroaromatic structures;

labels 1 and 2 mark the relevant positions on the A ring;
the X atom is selected from N (nitrogen) and C (carbon);

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R is a substituting group on the A ring selected from :

- a group in the 3 (meta) position selected from a linear or branched C₁-C₅ alkyl, C₂-C₅-alkenyl or C₂-C₅-alkynyl group, substituted or not-substituted phenyl, linear or branched C₁-C₅ hydroxyalkyl, C₂-C₅-acyl, substituted or not-substituted benzoyl;
- 5 - a group in the 4 (para) position selected from C₁-C₅ alkyl, C₂-C₅-alkenyl or C₂-C₅-alkynyl group, C₃-C₆-cycloalkyl, C₁-C₅-acyloxy, substituted or not-substituted benzoyloxy, C₁-C₅-acylamino, substituted or not-substituted benzoylamino, C₁-C₅-sulfonyloxy, substituted or not-substituted benzenesulfonyloxy, C₁-C₅-alkanesulfonylamino, substituted or not-substituted benzenesulfonylamino, C₁-C₅-alkanesulfonylmethyl, substituted or not-substituted benzenesulfonylmethyl, 2-furyl;
- 10 3-tetrahydrofuryl; 2- thiophenyl; 2-tetrahydrothiophenyl groups or a C₁-C₈-alkanoyl, cycloalkanoyl or arylalkanoyl-C₁-C₅-alkylamino group;

Hy is a small hydrophobic group with a steric hindrance factor ν ranging between 0.5 and 0.9 Å (where ν is the Charton steric constant for substituents), including methyl,

15 ethyl, chlorine, bromine, methoxy, trifluoromethyl;

Y is NH and R' is a residue of formula SO₂Rd wherein Rd is C₁-C₆-alkyl, C₁-C₆-cycloalkyl, C₁-C₆-alkenyl.

7. Compounds according to claim 1, selected from:

- (3-benzoyl-2-methylphenyl)acetic acid
- 20 (2-chloro-3-propionylphenyl)acetic acid
- (3-isopropyl-2-methylphenyl)acetic acid
- (4-isobutyl-2-methylphenyl)acetic acid
- {2-methyl-4-[(phenylsulphonyl)amino]phenyl}acetic acid
- {2-methyl-4-[(trifluoromethanesulphonyl)amino]phenyl}acetic acid
- 25 {2-chloro-4-[(trifluoromethanesulphonyl)oxy]phenyl}acetic acid
- (5-acetyl-1-methyl-1H-pyrrol-2-yl)acetic acid
- [1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl]acetic acid
- (5-benzoyl-1-methyl-1H-pyrrol-2-yl)acetic acid
- [1-methyl-5-(4-chlorobenzoyl)-1H-pyrrol-2-yl]acetic acid
- 30 (5-isobutyryl-1-methyl-1H-pyrrol-2-yl)acetic acid
- (1-benzoyl-2-methyl-1H-pyrrol-3-yl)acetic acid
- (1-benzoyl-2-chloro-1H-pyrrol-3-yl)acetic acid

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- (1-benzoyl-2-methyl-1H-indol-3-yl)acetic acid
[1-(4-chlorobenzoyl)-2-methyl-1H-indol-3-yl]acetic acid
(1-isopropyl-2-methyl-1H-pyrrole[2,3-b]pyridin-3-yl)acetic acid
(4-benzoyl-3-methyl-thien-2-yl)acetic acid
5 (5-acetyl-4-methyl-pyridin-3-yl)acetic acid
(5-benzoyl-4-methyl-pyridin-3-yl)acetic acid
(4-acetyl-3-methyl-pyridin-2-yl)acetic acid
(4-benzoyl-3-methyl-pyridin-2-yl)acetic acid
(4-acetyl-3-chloro-pyridin-2-yl)acetic acid
10 (4-benzoyl-3-chloro-pyridin-2-yl)acetic acid
(5-acetyl-4-chloro-pyridin-3-yl)acetic acid
(5-benzoyl-4-chloro-pyridin-3-yl)acetic acid
(3-benzoyl-2-methoxyphenyl)acetic acid
(5-acetyl-1-methyl-1H-pyrrol-2-yl)acetamide
15 (5-acetyl-1-methyl-1H-pyrrol-2-yl)acetyl methanesulphonamide
(5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-carboxymethylacetamide
(S)(5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-(2-carboxyethyl)acetamide
(5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-(3-dimethylaminopropyl)acetamide
(S)(5-acetyl-1-methyl-1H-pyrrol-2-yl)-N-(3-methoxy-2-carboxypropyl)acetamide
20 (4-isobutyl-2-methylphenyl)acetamide
(4-isobutyl-2-methylphenyl)acetyl methanesulphonamide
(2-chloro-3-propionylphenyl)-N-(3-dimethylaminoethyl)acetamide
(3-isopropyl-2-methylphenyl)-N-[3-(1-piperidinyl)propyl]acetamide
(3-benzoyl-2-methylphenyl)acetamide
25 (1-benzoyl-2-methyl-1H-indol-3-yl)acetamide
(1-benzoyl-2-methyl-1H-indol-3-yl)-N-(3-dimethylaminopropyl)acetamide
[1-(4-chlorobenzoyl)-2-methyl-1H-indol-3-yl]acetamide
[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetamide
{2-methyl-4-[(trifluoromethanesulphonyl)amino]phenyl} acetyl methanesulphonamide
30 {2-chloro-4-[(trifluoromethanesulphonyl)oxy]phenyl} N-(2-hydroxyethoxyethyl)acetamide
(1-benzoyl-2-methyl-1H-pyrrol-3-yl)-N-(2-methoxyethyl)acetamide

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(1-benzoyl-2-chloro-1H-pyrrol-3-yl)-N-[3-(1-morpholino)propyl]acetamide

(5-isobutyl-1-methyl-1H-pyrrol-2-yl)acetamide

[1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl]acetylmethanesulphonamide

(5-benzoyl-1-methyl-1H-pyrrol-2-yl)-N-(2-carboxymethyl)acetamide

5 [1-methyl-5-(4-chlorobenzoyl)-1H-pyrrol-2-yl]-N-(2-hydroxyethoxyethyl)acetamide

[1-methyl-5-(4-chlorobenzoyl)-1H-pyrrol-2-yl]acetamide

{2-methyl-4-[(phenylsulphonyl)amino]phenyl}-N-(3-dimethylaminopropyl)acetamide

(4-benzoyl-3-methyl-thien-2-yl)acetamide

(5-acetyl-4-methyl-pyridin-3-yl)acetamide

10 (5-acetyl-4-methyl-pyridin-3-yl)acetyl hydrossamic acid

(3-benzoyl-2-methoxyphenyl)acetamide.

8. Process for the preparation of compounds of formula (I) according to claim 6, comprising the transformation a compound of formula (I) wherein YR' is OH in a reactive intermediate, such as an acyl chloride or an ester with hydroxybenzotriazole, and reacting with a compound of formula $\text{NH}_2\text{SO}_2\text{Rd}$, wherein Rd is $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-cycloalkyl}$, $\text{C}_1\text{-C}_6\text{-alkenyl}$, in the presence of a suitable base, such as potassium tert-butoxide.

9. Pharmaceutical compositions comprising a compound according to any of claims 1 to 7 in admixture with a suitable carrier thereof.

20 10. Compounds according to any of claims 1 to 7 for use in the treatment of psoriasis, ulcerative colitis, melanoma, chronic obstructive pulmonary disease (COPD), bullous pemphigoid, rheumatoid arthritis, idiopathic fibrosis, glomerulonephritis and in the prevention and treatment of damages caused by ischemia and reperfusion.

25 11. Use of a compound according to any of claims 1 to 5 in the preparation of a medicament for the treatment of psoriasis, ulcerative colitis, melanoma, chronic obstructive pulmonary disease (COPD), bullous pemphigoid, rheumatoid arthritis, idiopathic fibrosis, glomerulonephritis and in the prevention and treatment of damages caused by ischemia and reperfusion.

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ABSTRACT

Selected 2-arylacetic acids, their derivatives and pharmaceutical compositions that contain these compounds are useful in inhibiting chemotactic activation of neutrophils (PMN leukocytes) induced by the interaction of Interleukin-8 (IL-8) with CXCR1 and CXCR2 membrane receptors. The compounds are used for the prevention and treatment of pathologies deriving from said activation. In particular, 2(ortho)-substituted arylacetic acids or their derivatives, such as amides and sulfonamides, lack cyclo-oxygenase inhibition activity and are particularly useful in the treatment of neutrophil-dependent pathologies such as psoriasis, ulcerative colitis, melanoma, chronic obstructive pulmonary disease (COPD), bullous pemphigoid, rheumatoid arthritis, idiopathic fibrosis, glomerulonephritis and in the prevention and treatment of damages caused by ischemia and reperfusion.

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Hydrophobic Aliphatic

HBA Projected Point 1

HBA Origin 1

HBA Origin 2

Hydrophobic Aromatic

HBA Projected Point 2

Figure 1

Hydrophobic Aliphatic

Hydrophobic Aromatic

HBA Origin 1

HBA Projected Point 1

HBA Origin 2

HBA Projected Point 2

Figure 2

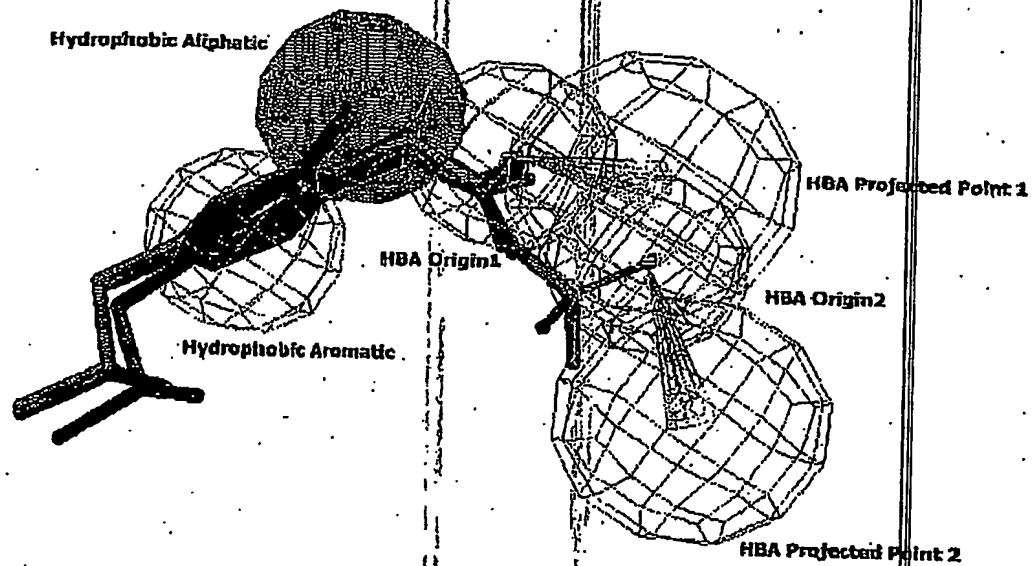


Figure 3

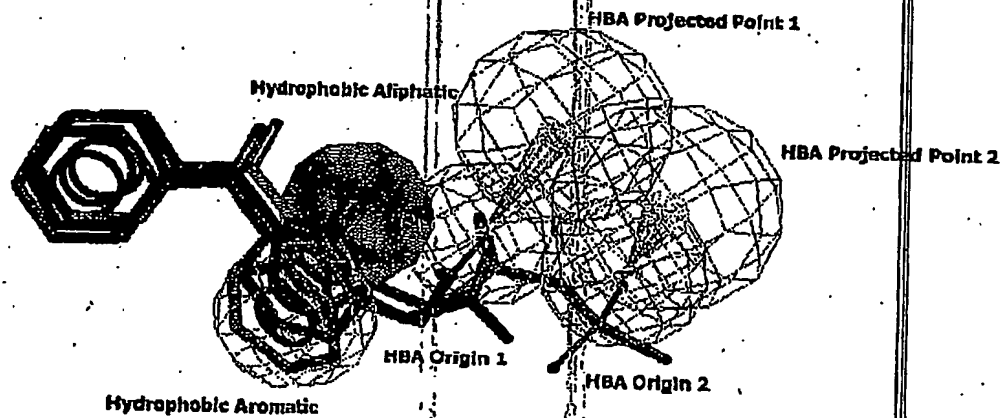


Figure 4

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